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Trial-to-Trial Variance in Choice Reaction Time as a Measure of the Effect of Stimulants During Sleep Deprivation

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Performance stability, as assessed by trial-to-trial variance in a choice reaction time (RT) task, was evaluated as a measure of stimulant effects on performance during sleep deprivation. Administration of methylphenidate, pemoline, and a placebo began 16 hr into a 64-hr sleep-deprivation protocol. Performance stability deteriorated significantly, especially during the circadian nadirs. In absolute terms, sleep deprivation increased trial-to-trial variance more than it increased the mean correct RT. In addition, this measure demonstrated differing effects of the 2 drug regimens. Pemoline, at a dose of 37.5 mg every 12 hr, significantly reduced the overall average effects of sleep loss on performance stability during the first 24 hr of drug administration. Pemoline also reduced circadian-related instability in performance throughout the study. Methylphenidate, at a dose of 10 mg every 6 hr, counteracted circadian-related instability in performance during the first 24-hr period of drug administration (16-40 hr of sleep deprivation) but not during the second 24-hr period (40-64 hr of sleep deprivation). Methylphenidate did not significantly affect the overall average effects of sleep loss on performance stability. Thus, trial-to-trial variance appears to be a valuable measure for elucidating stimulant effects during sleep deprivation.

Long-term sleep deprivation results in decrements in cognitive and psychomotor performance. Linear decreases in performance related to sleep deprivation are

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accompanied by circadian oscillations, with peaks around 1400 to 2000 and troughs between 0000 and 0600 (Babkoff, Caspy, Mikulincer, & Sing, 1991; Horne, 1988; Minors & Waterhouse, 1981). The amount of performance decrement that occurs during sleep deprivation depends on various stimuli and environmental variables (e.g., see Babkoff et al., 1991; Johnson, 1982). Different tasks show differing sensitivities to sleep loss (Babkoff et al., 1991; Dinges & Kribbs, 1991; Johnson, 1982). Several studies have attempted to clarify the mechanisms responsible for performance deficits during sleep loss as well as to test for solutions (Babkoff & Krueger, 1992).

Various pharmacological interventions have been proposed for maintaining performance during sleep deprivation, including hypnotics (to promote sleep before or after a prolonged work period) and stimulants such as amphetamines, methylphenidate, nicotine, 1-deprenyl, caffeine, pemoline, and modafinil (Babkoff & Krueger, 1992; Caldwell, Caldwell, Crowley, & Jones, 1995; Kelly, Ryman, Schlangen, Gomez, & Elsmore, 1997; Krueger, 1989; Krueger & Englund, 1985; Lagarde & Batejat, 1995; Newhouse et al., 1992; Nicholson & Turner, 1998; O'Donnell et al., 1988). Although amphetamines may ameliorate the effects of sleep deprivation, their side effects, which include short-term modification of the cardiovascular system (e.g., increased blood pressure and possible long-term abuse of the drug), may argue against their use. Several other stimulants (e.g., methylphenidate and pemoline) are medically approved and have been used extensively in the treatment of attention deficit disorder and narcolepsy (Conners & Taylor, 1980; Mitler, Shafor, Hajdukovic, Timms, & Browman, 1986).

We have argued that studies of substances to counteract performance deficit during sleep loss should include a variety of cognitive tasks. Because the sensitivity to sleep loss may differ from one cognitive function to another, the only way to obtain a broad view of the effect of a putative countermeasure is to study its impact on a large number of cognitive and psychomotor functions (e.g., see Babkoff et al., 1992; Babkoff & Krueger, 1992). A similar argument can be made for the inclusion of multiple performance measures on a given task. Results from a number of studies have shown that different measures of performance, even in a single task, may be differentially sensitive to sleep loss. For example, errors of omission and reaction times (RTs) may be more sensitive to sleep loss than errors of commission and accuracy (Babkoff et al., 1991; Johnson, 1982). Therefore, studies of pharmacological substances to counteract the effects of sleep loss should include a variety of performance measures to properly evaluate the impact of the treatment on performance deficit.

The performance measures most commonly reported in studies of sleep deprivation are measures of central tendency, for example, means, medians, or both. Although interindividual variances often are reported along with the means (population standard deviations), very few studies have analyzed and reported intraindividual variance. Intraindividual variance expresses the range of trial-to-trial changes in an individual participant's responses and, thus, provides a

measure of performance stability. Some researchers have proposed that the average performance of a participant may be less affected by sleep deprivation than the trial-to-trial variance (Dinges & Kribbs, 1991). This suggests that studies of the effects of drugs on performance during sleep loss should include an examination of performance stability.

RT tasks are a favorite dependent variable in studies of performance during sleep deprivation (Dinges & Kribbs, 1991; Johnson, 1982). Mean RT has been reported by many researchers to increase after as little as 24 to 36 hr of sleep deprivation (e.g., see Babkoff et al., 1991; Dinges & Kribbs, 1991; Johnson, 1982). However, very few studies have reported the effects of sleep deprivation on performance stability in choice RT. In this article, we examine the changes in trial-to-trial variance in the four-choice RT task during 64 hr without sleep and the impact of methylphenidate or pemoline on these changes. The four-choice RT data were selected for this analysis because a large number of trials were conducted, which provides a stable database for comparisons and conclusions.

METHOD

Methodology was reported in detail in a previous publication of data from this study (Babkoff et al., 1992) and will only be summarized here.

Participants

Thirty-six male students in the Basic Underwater Demolition and Seal (BUDS) training program in the U.S. Navy took part in this double-blind experiment. Average age was 20.94 years old (± 2.75 years). Participants were medication free, non-smokers, and light caffeine users.

Stimulants

Methylphenidate and pemoline were selected as established stimulants providing possible alternatives to amphetamines. Methylphenidate (Ritalin®) is a piperidine derivative that is thought to activate the brain stem arousal system and cortex, but its actual mechanism of action in humans has not yet been proven. It is classified as a mild central nervous system stimulant, and it is often prescribed for children suffering from attention deficit disorder and adults suffering from narcolepsy. Pemoline (Cylert®) is a dopaminergic oxazolidine compound, thought to act primarily through catecholamine uptake inhibition in the central nervous system. It also is prescribed for patients with narcolepsy and has an established history of medical use without a history of abuse (Connors & Taylor, 1980; Langer, Sweeney, Bartenbach, Davis, & Menander, 1986). Earlier reports indicated that pemoline can

improve alertness and performance in both well-rested and sleep-deprived participants (Babkoff et al., 1992; Nicholson & Pascoe, 1990; Nicholson & Turner, 1998). Although there may be long-term hepatic effects of the cumulative use of pemoline, short-term use is only contraindicated in people with hepatic failure (*Physician's Desk Reference*, 1999).

The participants were randomly assigned in equal numbers to one of the three groups—placebo, methylphenidate, or pemoline—in a parallel-group, double-blind design. All participants received eight drug–placebo administrations during the 64 hr of sleep deprivation beginning at 2200 of the first night (16 hr after awakening and at the beginning of the experiment). Participants in the placebo group received one placebo capsule every 6 hr. Participants in the methylphenidate group received a 10-mg capsule of methylphenidate every 6 hr. Participants in the pemoline group received a 37.5-mg capsule of pemoline every 12 hr and placebo capsules at the other four 6-hr intervals.

Performance Task

The data presented are for four-choice RT, a psychomotor task (Wilkinson & Houghton, 1975). On each trial, a star was displayed at one of four positions. The four stimulus positions form a square. The response buttons also were arranged in a square, and the participant was instructed to press the button whose position corresponded to that of the star. The task was participant-paced. Each stimulus was displayed until the participant responded, after which the next stimulus was immediately presented. Participants were tested using their preferred hand. Task duration was 11 min.

Four-choice RT was one of six tasks used in this study. Participants learned and practiced the computerized cognitive testing battery on Monday morning and were tested for baseline performance levels in the afternoon, after which practice continued until the evening. Participants slept in the laboratory Monday night and began the sleep deprivation period at 0620 Tuesday morning. Testing sessions occurred once every 3 hr and lasted approximately 2 hr. The last testing session ended at 2200 Thursday night. The total time without sleep was approximately 64 hr. Drug or placebo administration in all groups began at 2200 Tuesday night, the first night of sleep deprivation.

Statistical Analyses

Analyses of variance (ANOVAs) of the baseline four-choice RT data during the first 16 hr of the experiment, prior to the administration of drugs or placebos, revealed no differences among the groups. All of the analyses reported here include the data for the 16 sessions from the beginning of the administration of the placebo or drug until the end of the experiment. These sessions cover the two sequential 24-hr periods be-

ginning at 2200 on Tuesday night. For ease of reading, the two time periods will be referred to in the remainder of this article as Day 1 (2200 Tuesday to 2200 Wednesday; 16–40 hr of wakefulness) and Day 2 (2200 Wednesday to 2200 Thursday; 40–64 hr of wakefulness). It could be argued that these time periods really do represent the first and second 24-hr periods of true sleep deprivation. We generally do not consider ourselves to be sleep deprived when we go to bed after an ordinary day but only after we have missed some of our usual sleep. The start of drug administration coincided with the time when participants actually started missing sleep.

There were three levels of analysis. Initially, the trial-to-trial variance data were analyzed by repeated measures ANOVAs, with day and hour of the day as within factors and drug–placebo conditions as between factors. Then, trial-to-trial standard deviations were plotted against mean RT, and the data for each group were analyzed by regression analysis. All paired comparisons were subjected to two-tailed tests. Finally, coefficients of variation were calculated for each participant by dividing trial-to-trial variance by mean RT for the data of each session (Luce, 1986). We considered the coefficient of variation to be a more stable measure of performance stability because both mean RT and trial-to-trial variance change during sleep deprivation. These data were plotted against day and time, and the averaged data for each group were subjected to the time-series analysis, complex demodulation, to determine the composition of and the effects of the drugs on the rhythmic components.

Data generated in studies of sleep deprivation extending beyond 24 hr are characterized by monotonic and rhythmic changes over time (see Babkoff et al., 1992; Monk et al., 1985). A variety of time-series analyses have been described in detail and have been used to evaluate performance during sleep deprivation (Babkoff et al., 1991; Babkoff, Genser, Thorne, & Hegge, 1985; Monk et al., 1985; Naitoh, Englund, & Ryman, 1985). We chose complex demodulation as the time-series analysis most appropriate for our data because it allows for the possibility of changes in parameters over time (see Babkoff et al., 1991). Because the time series of interest is 48-hr long (from the first administration of the placebo or drug until the end of the experiment), it is legitimate to use complex demodulation to assess the circadian and hemicircadian components from the residual data after subtracting the linear trend (Babkoff et al., 1991). The rationale and methodology for the use of complex demodulation are beyond the scope of this article and have been presented in detail in earlier articles (Babkoff et al., 1992; Sing, Thorne, Hegge, & Babkoff, 1985).

RESULTS

Mean Correct RT

The mean correct and error RT data were reported in detail in a previous publication (Babkoff et al., 1992). The results for the mean RT for the correct responses will be

summarized here.¹ Mean correct RT is plotted in Figure 1 for the placebo, methylphenidate, and pemoline groups. There was a general increase in RT ($p < .0001$) during sleep deprivation as well as very clear circadian swings ($p < .0001$). There was also a significant interaction between hours of wakefulness and the hour of the day. The circadian variation was significantly increased during the second night and early morning, after 44 hr of wakefulness (Day \times Hour of the Day, $p < .005$). There were no significant drug effects on mean correct RT.

Intraparticipant Variance

The average intraparticipant trial-to-trial standard deviations for each group, beginning with the first administration of the drugs or placebo until the end of the experiment, are plotted in Figure 2. The trial-to-trial standard deviation increased across hours of sleep deprivation, $F(1, 23) = 48.25, p < .0001$. In addition, there were significant circadian changes, $F(7, 161) = 5.85, p < .0001$. There was also a significant interaction—that is, the circadian change in standard deviation was greater during Day 2 than during Day 1—Day \times Hour of the Day, $F(7, 161) = 2.98, p < .05$. The trial-to-trial standard deviations were significantly smaller for participants receiving the drugs than for participants receiving the placebo, $F(2, 23) = 4.37, p < .05$. There was a Drug \times Day \times Hour of the Day interaction, $F(14, 161) = 2.21, p < .01$, that appears to reflect reduced trial-to-trial standard deviations at the circadian trough during Day 2 for the pemoline group (see Figure 2).

Trial-to-Trial Variance Versus Mean Correct RT

The average trial-to-trial standard deviations on each session are plotted as a function of the average RT for that session for the placebo, methylphenidate, and

¹Because the trial-to-trial variance of reaction time (RT) for correct responses, but not incorrect responses, responded to the drug treatment, correct RT variance is the focus of this article. We summarize the results for the error RT here. Mean error RT responded to drug treatment in a manner similar to mean correct RT (Babkoff et al., 1992). There was a general increase in error RT ($p < .0001$) during sleep deprivation as well as very clear circadian swings ($p < .0001$). There was no main effect of drug on error RT. As with correct RT, the overall increase in error RT found on Day 2 was not significantly reduced by either drug. However, the Hour of the Day \times Drug interaction was significant for the error RT ($p < .0136$). Thus, for error responses, the drugs significantly reduced the circadian increase in RT (Babkoff et al., 1992). The trial-to-trial standard deviations for error RT increased across hours of sleep deprivation, $F(1, 23) = 10.17, p < .005$, and showed significant circadian changes, $F(7, 161) = 2.77, p < .01$. There was also a significant interaction; that is, the circadian change in standard deviation was greater during Day 2 than during Day 1 for error RT, $F(7, 161) = 2.35, p < .05$. The drugs did not significantly reduce the trial-to-trial standard deviations for error RT, $F(2, 23) = 1.63, ns$, and there were no significant interactions of Drug \times Day or Drug \times Hour of the Day for error-RT variance.

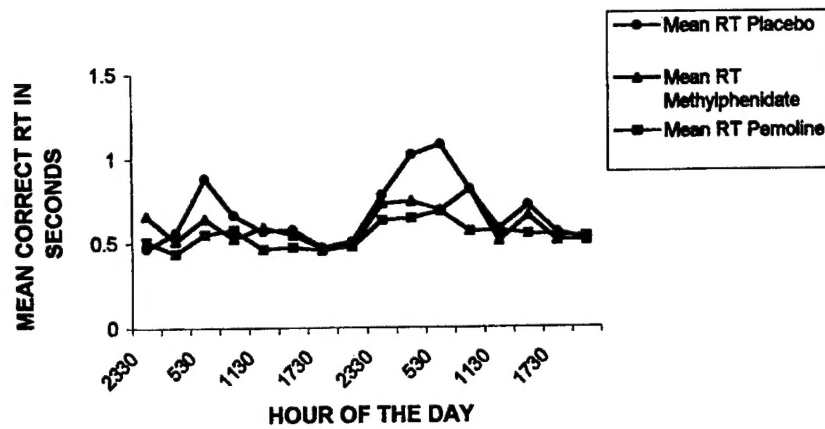


FIGURE 1 Mean correct choice reaction time during Day 1 and Day 2 (16–64 hr) of sleep deprivation.

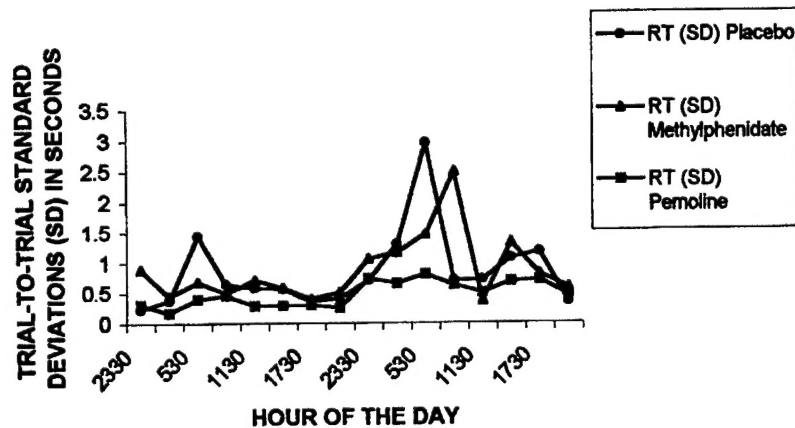


FIGURE 2 Trial-to-trial variance (standard deviations) in correct reaction time during Day 1 and Day 2 of sleep deprivation.

pemoline groups in Figure 3 (Day 1) and Figure 4 (Day 2), along with the best linear fits. The characteristics of the best fitting linear regressions are shown in Table 1. For all of the groups, the linear regression was highly significant on Day 1, explaining between 86% to 94% of the variance. During Day 2, the linear model was significant for the placebo group, $F(1, 6) = 6.75, p < .05$, and the methylphenidate group, $F(1, 6) = 14.6, p < .01$, in which it explained 53% to 71% of the variance, but it was not significant for the pemoline group, $F(1, 6) = 4.27, p < .084$ (see Figure 4).

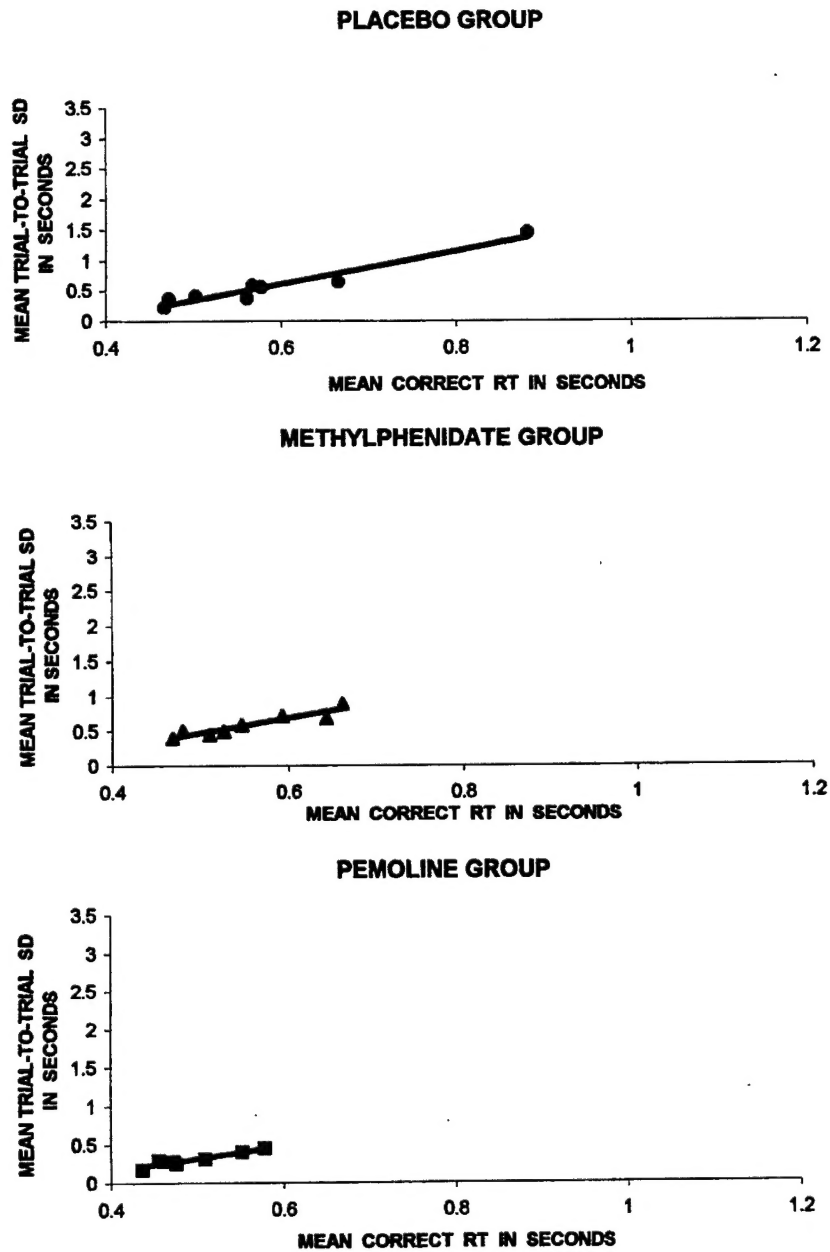


FIGURE 3 Trial-to-trial variance (correct reaction time) plotted as a function of mean reaction time for sessions of Day 1 (16-40 hr) of sleep deprivation.

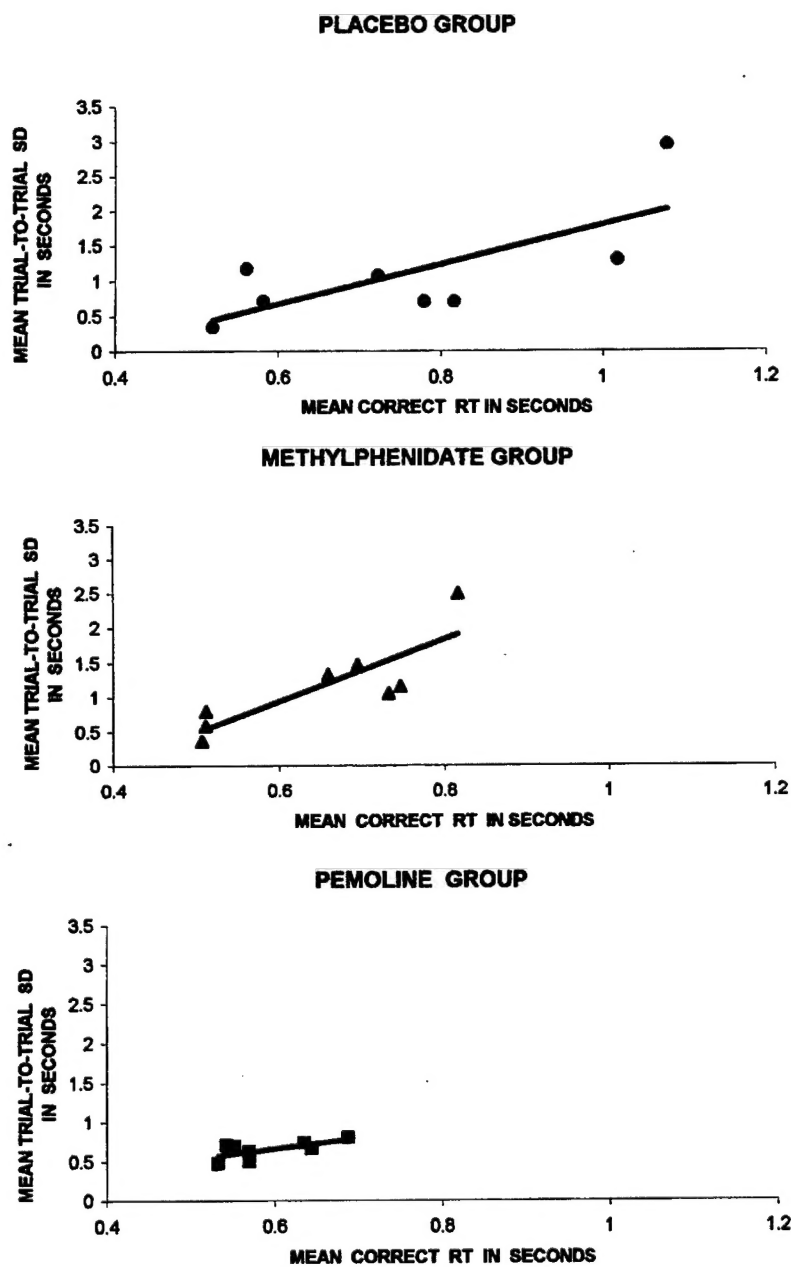


FIGURE 4 Trial-to-trial variance (correct reaction time) plotted as a function of mean reaction time for sessions of Day 2 (40–64 hr) of sleep deprivation.

TABLE 1
Linear Regression: Trial-to-Trial Standard Deviation Plotted Against Mean Reaction Time

	Placebo	Methylphenidate	Pemoline
Day 1 (16–40 hr of sleep deprivation)			
Linear slope	2.703	2.096	1.627*
Upper 95% confidence limits	3.388	2.914	2.273
Lower 95% confidence limits	2.018	1.279	0.981
	$R = .969$	$R = .932$	$R = .929$
F (linearity)	$F = 93.11, p < .0001$	$F = 39.37, p < .0008$	$F = 37.98, p < .0008$
Day 2 (40–64 hr of sleep deprivation)			
Linear slope	2.808	4.514	1.306
Upper 95% confidence limits	5.455	7.405	2.853
Lower 95% confidence limits	0.163	1.623	-0.241
	$R = .727$	$R = .840$	$R = .644$
F (linearity)	$F = 6.75, p < .04$	$F = 14.60, p < .009$	$F = 4.27, p < .084$

* $p < .05$.

For Day 1, the slope of the linear regression for the group receiving pemoline was significantly less than that of the placebo group ($p < .05$; see Table 1 and Figure 3), and there was only a trend for the slope of the methylphenidate group to be less steep than that of the placebo group ($p < .10$; see Table 1 and Figure 3). Thus, although trial-to-trial standard deviations increased with increasing mean RT in all groups during Day 1, the relative increase was significantly less for the participants receiving pemoline, as compared to those receiving the placebo. On Day 2, however, there was no significant difference in the slopes among the groups (Table 1). Because of the high variance in the placebo and methylphenidate groups, the linear component of the slope of the pemoline group falls within the 95% confidence interval of the placebo group.

Coefficient of Variation and Complex Demodulation

The average coefficient of variation for the pemoline group (0.608) was significantly different from that of the placebo and methylphenidate groups (0.919 and 1.046, respectively) on Day 1, $F(2, 21) = 7.55, p < .005$. The coefficients of variation on Day 2 (1.404 for the placebo, 1.696 for the methylphenidate, and 1.097 for the pemoline) differed significantly from Day 1 for each of the groups but did not differ significantly among the groups.

The rhythmic components of the coefficients of variation were analyzed by complex demodulation after regression analysis identified the best fitting linear slope (Babkoff et al., 1991; Sing et al., 1985). The linear equation is most easily understood as representing the change in the coefficient of variation from Day 1

to Day 2. The remodulate frequencies generated by complex demodulation are the smoothed functions of the rhythmic components assessed from the data and represent the best fitting models of those frequencies when plotted against time (Sing et al., 1985). The percentage of variance accounted for by the three components during sleep deprivation are shown in the upper part of Table 2 for each group. The circadian component contributed most to the changes in the coefficient of variation for participants receiving either the placebo or methylphenidate (30.84% and 31.58%, respectively), and the linear component contributed relatively less for these participants (13.48% and 16.75%, for placebo and methylphenidate, respectively). In contrast, the linear component accounted, by far, for most of the changes in the coefficient of variation for participants receiving pemoline (56.76%), whereas the circadian component contributed less (18.52%) to the explained variance. The hemicircadian component contributed the least for the methylphenidate group, followed by the placebo group; it contributed most to the variation in the pemoline group (8.65%–18.35%).

The best fitting circadian remodulates of the averaged group data are shown in Figure 5. The average deviations around zero of the circadian remodulate of the coefficient of variation for the participants receiving methylphenidate and pemoline are compared to those for the participants receiving the placebo (marked as 100% in the lower part of Table 2). The participants who received methylphenidate and pemoline differed significantly from participants who received the placebo on Day 1: Methylphenidate versus placebo = 63%, $t(15) = 2.201$, $p < .05$, and pemoline versus placebo = 22%, $t(15) = 4.845$, $p < .001$ (see Table 2). On Day 2, the average deviations in the circadian remodulate for participants who received methylphenidate was 96% as great as the deviation seen in participants who received the placebo, $t(15) = 0.154$, ns , and that of the participants who received pemoline was 35% as great, $t(15) = 4.525$, $p < .001$.

TABLE 2
Complex Demodulation of the Coefficient of Variation

	Placebo	Methylphenidate	Pemoline
Percentage of variance explained			
Linear	13.38	16.75	56.76
Circadian	30.84	31.58	18.52
Hemicircadian	13.29	8.60	18.35
Total	57.51	56.93	93.63
Average deviations in circadian remodulate (compared to placebo)			
Day 1	100%	63%*	22%**
Day 2	100%	96%	35%**

* $p < .05$. ** $p < .001$.

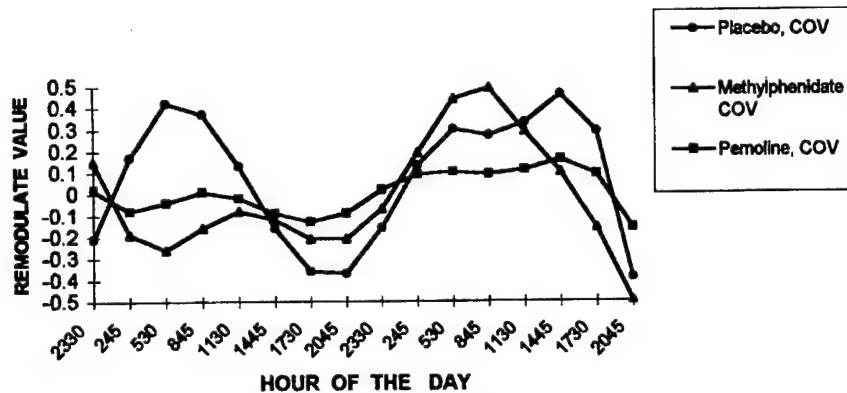


FIGURE 5 Circadian remodulate of coefficient of variation for sessions of Days 1 and 2 (16-64 hr) of sleep deprivation.

DISCUSSION

Performance Stability and Sleep Deprivation

Performance stability as measured by trial-to-trial RT variance deteriorated significantly during the 64 hr of sleep deprivation and especially during the circadian nadirs. In absolute terms, sleep deprivation increased trial-to-trial variance more than it increased the mean RT (compare Figure 1 with Figure 2). The data show that the increase in trial-to-trial variance due to the circadian rhythm was greater during Day 2 than Day 1, with the largest trial-to-trial standard deviations occurring during the second circadian nadir after approximately 46 hr without sleep.

One of the almost ubiquitous features of RT distributions during long-term sleep deprivation is the increased frequency of very long RTs (Babkoff et al., 1991; Babkoff et al., 1985; Dinges & Kribbs, 1991). In fact, several authors have argued that the very long RTs are the major contributor to the longer mean RTs that are reported by most researchers of sleep deprivation (Williams, Lubin, & Goodnow, 1959). Very long RTs in participant-paced tasks are considered to be the counterpart of "lapses" in experimenter-paced tasks (Dinges & Kribbs, 1991). The increased frequency of very long RTs causes the distributions to become asymmetric, with a pronounced positive skew as sleep deprivation progresses. According to this interpretation, the increased skew of the RT distribution is the major cause of increased trial-to-trial variance during sleep deprivation as well as the major contributor to increased mean RT (Dinges & Kribbs, 1991).

A recent study examined performance on a simulated driving task at 0800, 1100, 1400, 1700, and 2000 after one night of sleep deprivation (Lenne, Triggs, &

Redman, 1998). Comparing sleep-deprived participants to participants who had slept the night before, that study found increases in the standard deviations for maintenance of a lateral position and speed as well as in the average values of lateral position and speed. Thus, the authors reported a main effect of sleep loss in reducing performance stability, consistent with our findings. In contrast, Lenne et al. found no interaction between sleep deprivation and time of day on performance stability. However, that study only tested participants during the usual waking hours of the day. The major effects of the circadian rhythms during sleep deprivation are seen at the circadian nadir during the early morning hours (Babkoff et al., 1991; Dinges & Kribbs, 1991; Johnson, 1982). Therefore, the effects of circadian rhythms really could not be assessed in that study. In the experiment reported here, performance stability was tested around the clock during 64 hr of sleep deprivation, and the findings support the conclusion that sleep loss interacts with circadian rhythms to cause further deterioration in performance stability.

Stimulants and Performance Stability

The design of this study does not allow a definitive comparison of the effects of methylphenidate and pemoline on performance stability during sleep loss because only one dose level was used for each drug. The results presented here do, however, demonstrate the ability of a measure of performance stability to elucidate differing stimulant effects during sleep deprivation. In the following discussion, we compare the effects of the drugs at the levels tested to illustrate the interaction of the stimulants with the monotonic and rhythmic components of performance stability during sleep deprivation.

Mean correct RT, as a measure, was unable to detect any effects of either methylphenidate or pemoline at the doses and administration schedule used. The drugs did not significantly reduce overall mean correct RT during 64 hr of sleep deprivation. In addition, they did not attenuate the increase in mean correct RT from Day 1 to Day 2 (Babkoff et al., 1992). In contrast, performance stability, as measured by trial-to-trial variance, showed very clear drug effects. The drugs significantly reduced trial-to-trial variance, especially during Day 1, either in terms of the overall average variance, presumably by acting directly on the effects of accumulated wakefulness, or by acting against the circadian changes. Furthermore, the group receiving pemoline showed less of an increase in trial-to-trial variance at the circadian trough during Day 2 (see Figure 2).

Mean RT and trial-to-trial standard deviations covary over much of the range of response times. As a general rule, the longer the RT, the greater the trial-to-trial variance (Luce, 1986). Because of the asymmetry of RT distributions, the increased variance is most often caused by an increased number of long RTs. Although trial-to-trial standard deviations increased with increasing mean RT during sleep

deprivation in all the groups, the relative increase was significantly less for the participants receiving pemoline than for the participants receiving the placebo on Day 1. Thus, pemoline made the RT distributions less variable (i.e., with fewer long RTs) without significantly affecting the mean RT during Day 1. Methylphenidate showed only a trend for such an effect.

Because both mean RT and trial-to-trial variance increase during sleep deprivation, the coefficient of variation (standard deviation and mean RT) should provide a tighter measure of performance stability than the standard deviation alone. The coefficient of variation for simple RT has been reported to be around 0.1 or 0.2. When the signals are weak and mean RT is fairly long (approximately 1 sec), the coefficient of variation is larger (Luce, 1986). Consequently, coefficients of variation assessed for choice RT tasks are usually larger. In the experiment here, the coefficients of variation increased systematically from the beginning to the end of the 64 hr of sleep deprivation. The average coefficient of variation for the four-choice RT on the five sessions, during the first 16 hr of the experiment, was 0.469, which is similar to previous reports for choice RT tasks in non-sleep-deprived participants (0.4; see Luce, 1986). During Day 1, the coefficient of variation was significantly smaller for the pemoline group (0.608) than for the placebo and methylphenidate groups (0.919 and 1.045, respectively). During Day 2, the coefficients of variation of the participants in all groups exceeded 1.0 (1.40 for placebo, 1.69 for methylphenidate, and 1.09 for pemoline). This indicates that the increase in trial-to-trial variance was greater than the comparable increase in mean RT during this period.

The complex demodulation analysis of the coefficient of variation also highlights the differential effects of pemoline and methylphenidate on the two different sources of variance in sleep deprivation data: the monotonic and circadian components. Both methylphenidate and pemoline muted sleep deprivation's enhancement of the circadian rhythm effects on the coefficient of variation during Day 1. However, at the doses used in this study, pemoline did so more than methylphenidate did, and, on Day 2, only pemoline continued to mute sleep deprivation increases in the circadian rhythm of the coefficient of variation.

Thus, the findings lead us to conclude that pemoline ameliorated the deficit in performance stability during the sleep deprivation in two ways. Pemoline maintained the value of the coefficient of variation for up to 40 hr of sleep loss (Day 1). Pemoline also muted sleep-deprivation enhancement of circadian fluctuations in the coefficient of variation throughout the study (64 hr). Methylphenidate was only shown to decrease the enhanced circadian fluctuations during Day 1.

The average circadian deviations for participants receiving pemoline was 22% of that of participants receiving the placebo on Day 1 and 35% of participants receiving the placebo on Day 2 (see Figure 5 and Table 2). The average circadian deviations for participants receiving methylphenidate was 63% of that of participants receiving the placebo on Day 1 but increased to 96% of that of the participants receiving the placebo on Day 2 of sleep deprivation. Thus, although participants re-

ceiving methylphenidate were able to somewhat restrict the circadian variation in performance stability during the first 40 hr of sleep deprivation, those receiving pemoline were able to limit the circadian variation during the entire 64 hr of sleep deprivation.

In conclusion, trial-to-trial variation is a sensitive measure for assessing performance stability and the effects of stimulants during sleep deprivation. More specifically, the coefficient of variation (standard deviation and mean RT) was found to be an optimal measure of drug effect on performance stability, particularly in conjunction with complex demodulation. With the dosages used in this study, pemoline, but not methylphenidate, attenuated the overall effects of moderate sleep deprivation (up to 40 hr) on this measure of performance stability. Pemoline also caused a greater and more persistent decrease in circadian variation in performance stability than did methylphenidate. Pemoline decreased the effects of the circadian variation in performance stability during the entire 64 hr without sleep. Further testing of this measure with other drugs, other doses, and other tasks should be performed to confirm this as an optimal measure of stimulant effects during sleep deprivation.

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REFERENCES

- Babkoff, H., Caspy, T., Mikulincer, M., & Sing, H. C. (1991). Monotonic and rhythmic influences: A challenge for sleep deprivation research. *Psychological Bulletin*, 109, 411-428.
- Babkoff, H., Genser, S. G., Thorne, D. R., & Hegge, F. W. (1985). The effects of progressive sleep loss on a lexical decision task: Response lapses and response accuracy. *Behavior Research Methods, Instruments, and Computers*, 17, 614-622.
- Babkoff, H., Kelly, T. L., Matteson, L. T., Gomez, S. A., Lopez, A., Hauser, S., Naitoh, P., & Assmus, J. (1992). Pemoline and methylphenidate: Interaction with mood, sleepiness, and cognitive performance during 64 hours of sleep deprivation. *Military Psychology*, 4, 235-265.
- Babkoff, H., & Krueger, G. P. (1992). Use of stimulants to ameliorate the effects of sleep loss during sustained performance. *Military Psychology*, 4, 191-205.
- Caldwell, J. A., Caldwell, J. L., Crowley, J. S., & Jones, H. D. (1995). Sustaining helicopter pilot performance with dexedrine during periods of sleep deprivation. *Aviation, Space, and Environmental Medicine*, 66, 930-937.
- Conners, C. K., & Taylor, E. (1980). Pemoline, methylphenidate and placebo in children with minimal brain dysfunction. *Archives of General Psychiatry*, 37, 922-930.

- Dinges, D. F., & Kribbs, N. B. (1991). Performing while sleepy: Effects of experimentally-induced sleepiness. In T. M. Monk (Ed.), *Sleep, sleepiness and performance* (pp. 97-128). New York: Wiley.
- Horne, J. A. (1988). *Why we sleep*. New York: Oxford University Press.
- Johnson, L. C. (1982). Sleep deprivation and performance. In W. B. Webb (Ed.), *Biological rhythms, sleep, and performance* (pp. 111-131). New York: Wiley.
- Kelly, T. L., Ryman, D. H., Schlangen, K., Gomez, S. A., & Elsmore, T. F. (1997). The effects of a single dose of pemoline on performance and mood during sleep deprivation. *Military Psychology*, 9, 213-225.
- Krueger, G. P. (1989). Sustained work, fatigue, sleep loss and performance: A review of the issues. *Work and Stress*, 3, 129-141.
- Krueger, G. P., & Englund, C. E. (1985). Methodological approaches to the study of sustained work/sustained operations. *Behavior Research Methods, Instruments, and Computers*, 17, 587-591.
- Lagarde, D., & Batejat, D. (1995). Disrupted sleep-wake rhythm and performance: Advantages of Modafinil. *Military Psychology*, 7, 165-191.
- Langer, D. H., Sweeny, K. P., Bartenbach, D. E., Davis, P. M., & Menander, K. B. (1986). Evidence of lack of abuse or dependence following pemoline treatment: Results of a retrospective survey. *Drug Alcohol Dependency*, 17, 213-227.
- Lenne, M. G., Triggs, T. J., & Redman, J. R. (1998). Interactive effects of sleep deprivation, time of day, and driving experience on a driving task. *Sleep*, 21, 38-44.
- Luce, R. D. (1986). *Response times: Their role in inferring elementary mental organization*. Oxford, England: Oxford University Press.
- Minors, D. S., & Waterhouse, J. M. (1981). *Circadian rhythm and the human*. Bristol, England: Wright.
- Mitler, M. M., Shafor, F., Hajdukovic, R., Timms, R. M., & Browman, C. P. (1986). Treatment of narcolepsy: Objective studies on methylphenidate, pemoline and protriptyline. *Sleep*, 9, 260-264.
- Monk, T. H., Fookson, J. E., Kream, J., Moline, M. L., Pollack, C. P., & Weitzman, M. B. (1985). Circadian factors during sustained performance: Background and methodology. *Behavior Research Methods, Instruments, and Computers*, 17, 19-26.
- Naitoh, P., Englund, C. E., & Ryman, D. H. (1985). Circadian rhythms determined by cosine curve fitting: Analysis of continuous work and sleep-loss data. *Behavior Research Methods, Instruments, and Computers*, 17, 630-641.
- Newhouse, P. A., Penetar, D. M., Fertig, J. B., Thorne, D. R., Sing, H. C., Thomas, M. L., Cochran, J. C., & Belenky, G. L. (1992). Stimulant drug effects of performance and behavior after prolonged sleep deprivation: A comparison of amphetamine, nicotine, and deprenyl. *Military Psychology*, 4, 207-233.
- Nicholson, A. N., & Pascoe, P. A. (1990). Dopaminergic transmission and the sleep-wakefulness continuum in man. *Neuropharmacology*, 4, 411-417.
- Nicholson, A. N., & Turner, C. (1998). Intensive and sustained air operations: Potential use of the stimulant, pemoline. *Aviation, Space, and Environmental Medicine*, 69, 647-655.
- O'Donnell, V. M., Balkin, T. J., Andrade, J. K., Simon, L. M., Kamimon, G. H., Redmond, D. P., & Belenky, G. (1988). Effects of triazolam on performance and sleep in a model of transient insomnia. *Human Performance*, 1, 145-160.
- Physicians' desk reference* (52nd ed.). (1999). Montvale, NJ: Medical Economics.
- Sing, H. C., Thorne, D. R., Hegge, F. W., & Babkoff, H. (1985). Multiple complex demodulation: A method for rhythmic analysis of physiological and biological data. *Behavior Research Methods, Instruments, and Computers*, 17, 623-629.
- Wilkinson, R. T., & Houghton, D. (1975). Portable four-choice reaction time test with magnetic tape memory. *Behavior Research Methods and Instrumentation*, 7, 441-446.
- Williams, H. L., Lubin, A., & Goodnow, J. J. (1959). Impaired performance with acute sleep loss. *Psychological Monographs*, 73(14, Whole No. 484).

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Performance stability as assessed by trial-to-trial variance in a choice reaction time (RT) task, was evaluated as a measure of stimulant effects on performance during sleep deprivation. Administration of methylphenidate, pemoline, and a placebo began 16 hr into a 64-hr-sleep deprivation protocol. Performance stability deteriorated significantly, especially during the circadian nadirs. In absolute term, sleep deprivation increased trial-to-trial variance more than it increased the mean correct RT. In addition, this measure demonstrated differing effects of the 2 drug regimens. Pemoline, at a dose of 37.5 mg every 12 hr, significantly reduced the overall average effects of sleep loss on performance stability during the first 24 hr of drug administration. Pemoline also reduced circadian-related instability in performance throughout the study. Methylphenidate, at a dose of 10 mg every 6 hr, counteracted circadian-related instability in performance during the first 24-hr period of drug administration (16-40 hr of sleep deprivation) but not during the second 24-hr period (40-64 hr of sleep deprivation). Methylphenidate did not significantly affect the overall average effects of sleep loss on performance stability. Thus, trial-to-trial variance appears to be a valuable measure for elucidating stimulant effects during sleep deprivation

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